IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Enzalutamide – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Enzalutamid – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2013). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BPI-SF	Brief Pain Inventory – Short Form
BSC	best supportive care
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life-5 Dimensions
FACT-P	Functional Assessment of Cancer Therapy – Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
WHO	World Health Organization

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug enzalutamide. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 2 September 2013.

Research question

The aim of this report was to assess the added benefit of enzalutamide compared with best supportive care (BSC) as appropriate comparator therapy (ACT) in men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel chemotherapy.

Studies that investigated a comparison of enzalutamide with or without BSC versus BSC could be considered for the benefit assessment.

The assessment was conducted based on patient-relevant outcomes. One direct comparative randomized controlled trial (RCT) was included in the assessment.

Results

The AFFIRM study (the approval study of enzalutamide for the therapeutic indication to be assessed) was included in the assessment.

Study characteristics

The AFFIRM study is a randomized, double-blind, placebo-controlled study in men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel chemotherapy. 1199 patients were randomized in a ratio of 2:1, 800 patients in the enzalutamide arm and 399 in the placebo arm. Since BSC was not part of the randomized study treatment, it was investigated whether the patients in the placebo arm received concomitant therapy that sufficiently fulfilled the criteria of BSC. This investigation gave rise to uncertainties, especially in relation to pain therapy. In the first 13 weeks after the start of the study treatment, pain therapy was specified as a single long-acting narcotic analgesic, a drug for the treatment of breakthrough pain (rescue medication) and – if necessary – a non-steroidal anti-inflammatory drug. Deviations from the specified treatments regarding the concomitant therapy (and hence also the pain therapy) were only permitted if considered absolutely necessary for the patient's well-being; in this context, continuation of the patient in the study had to be agreed with the company's medical monitor. On the basis of this information, it is unclear whether adequate pain therapy was ensured for the patients over this period. For this reason, overall the AFFIRM study is subject to an increased level of

uncertainty. This was taken into account when deriving the added benefit, in that the probability was reduced by one level (e.g. from "indication" to "hint"). Despite the uncertainty, the treatment in the placebo arm of the study is hereinafter termed "BSC".

The study treatment was continued until the patient withdrew his or her declaration of consent, until the occurrence of safety concerns (e.g. unacceptable toxicity) or the occurrence of progression (bone metastases, soft tissue metastases or skeletal-related complication) and subsequent treatment with a systemic antineoplastic therapy. The median duration of treatment with the study medication was 8.3 months in the enzalutamide arm and 3.0 months in the placebo arm.

After the end of the study treatment, the patients first underwent a follow-up of up to 30 days to record adverse events (AEs) and thereafter a long-term follow-up every 12 weeks until the end of the study. The primary outcome was overall survival.

An interim analysis of the study after 520 deaths and a final analysis after 650 deaths were originally planned. The interim analysis was conducted after 520 deaths as intended and, because of the efficacy results, the recording of data was then stopped for all outcomes except overall survival and pharmacovigilance.

The results from the interim analysis were used for the benefit assessment.

Risk of bias

The risk of bias of the AFFIRM study at study level was rated as low.

At outcome level, the risk of bias for the outcomes "overall survival", "time to first skeletal-related complication" and "time to pain progression" was rated as low. For the outcome "change in pain intensity", the risk of bias was rated as high. The results on the included outcomes on AEs could only be interpreted in qualitative terms, because the marked differences in treatment duration of patients in the 2 treatment arms meant that the analyses based on naive proportions of patients with events were only evaluable for the benefit assessment to a limited extent.

Results

Mortality

Treatment with enzalutamide + BSC produced a statistically significant prolongation of overall survival compared with placebo + BSC. Based on the total population of the AFFIRM study, there was a hint of added benefit of enzalutamide + BSC compared with BSC for the outcome "overall survival". In addition, there was an indication of an effect modification for the outcome "overall survival" by the characteristic "visceral metastases at the time of screening" (interaction test: $p = 0.15$). It was therefore necessary to consider the results for patients with visceral or without visceral metastases separately.

In patients without visceral metastases, treatment with enzalutamide + BSC produced a statistically significant prolongation in overall survival compared with placebo + BSC. This provides a hint of added benefit of enzalutamide + BSC compared with BSC for patients without visceral metastases for the outcome "overall survival".

There was no statistically significant difference in terms of the duration of overall survival for the patients with visceral metastases. Hence, an added benefit for the subgroup of patients with visceral metastases is not proven for the outcome "overall survival".

Morbidity

The time to the first skeletal-related complication was statistically significantly longer under treatment with enzalutamide + BSC than under treatment with placebo + BSC. This provides a hint of added benefit of enzalutamide + BSC compared with BSC for the outcome "time to first skeletal-related complication". In addition, for this outcome there was an indication of an effect modification by the characteristic "age" (interaction test: $p = 0.199$). It was therefore also necessary to consider the results for patients < 65 years and ≥ 65 years separately. Treatment with enzalutamide + BSC produced a statistically significant prolongation in time to first skeletal-related complication compared with placebo + BSC, both for the patients < 65 years and also for the patients ≥ 65 years. This provides a hint of an added benefit of enzalutamide + BSC compared with BSC for both subgroups for the outcome "time to first skeletal-related complication".

The time to pain progression was statistically significantly longer under treatment with enzalutamide + BSC than under treatment with placebo + BSC. This provides a hint of added benefit of enzalutamide + BSC compared with BSC for the outcome "time to pain progression".

On the basis of the continuous data on the change in pain intensity, treatment with enzalutamide + BSC produced statistically significantly less pain compared with placebo + BSC. This provides a hint of added benefit of enzalutamide + BSC compared with BSC for the outcome "change in pain intensity".

The company's dossier contained no evaluable data on paralyses and paralysis-related urinary incontinence. Hence, an added benefit of enzalutamide + BSC compared with BSC in terms of the outcome "paralyses and paralysis-related urinary incontinence" is not proven.

Health-related quality of life

Since the company's dossier contained no evaluable data on health-related quality of life, an added benefit of enzalutamide + BSC compared with BSC in terms of the outcome "health-related quality of life" is not proven.

Adverse events

As regards severe AEs (CTCAE Grade ≥ 3), a statistically significant difference in favour of enzalutamide + BSC was shown on the basis of naive proportions. Under consideration of the known direction of bias, it is assumed that the statistically significant effect in favour of enzalutamide + BSC would persist on resolution of the bias. This provides a hint of a lesser harm of enzalutamide + BSC compared with BSC for the outcome "severe AEs" (CTCAE Grade ≥ 3).

As regards the outcomes "serious adverse events" (SAEs) and "treatment discontinuation due to AEs", on the basis of naive proportions, no statistically significant difference between the treatment arms was shown. In these cases, the only derivable conclusion is that despite the bias to the disadvantage of enzalutamide in the submitted data, no greater harm was shown. Hence, a greater or lesser harm of enzalutamide + BSC compared with BSC for SAEs and treatment discontinuation due to AEs is not proven.

No evaluable results were available for seizures. A greater or lesser harm of enzalutamide + BSC compared with BSC is not proven for this outcome.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

The overall conclusion on added benefit was derived separately for the 2 relevant subgroup characteristics "visceral metastases" and "age". On the basis of the results presented, the extent and probability of the added benefit of the drug enzalutamide in combination with BSC compared with the ACT are assessed as follows:

Subgroup characteristic "visceral metastases"

Based on the available and evaluable results, overall at outcome level only positive effects remain, each with the same probability (hint). These were shown in the outcome categories "mortality", "serious/severe symptoms/late complications", "serious/severe AEs" and "non-serious/non-severe symptoms/late complications". For the outcomes "time to first skeletal-related complication" and "time to pain progression", the extent is, in each case, considerable. The extent of added benefit for the outcomes "change in pain intensity" and "serious AEs" is non-quantifiable. The extent category "non-quantifiable" is an expression of the uncertainty regarding the effect size and can also include the extent category "major". However, in the present case, due to the respective effect sizes, it cannot be assumed that the threshold for the extent category "major" is reached. Overall, without consideration of the results that showed

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

an indication of an effect modification by the characteristic “visceral metastases”, there is thus first of all a hint of a considerable added benefit of enzalutamide + BSC compared with BSC.

For patients with visceral metastases, no additional positive or negative effects were shown, so that the overall conclusion (hint of a considerable added benefit) does not change for these patients. For patients without visceral metastases, there is also a hint of a considerable added benefit for the outcome “overall survival”. This also changes the overall conclusion on added benefit for these patients to a hint of a major added benefit.

Subgroup characteristic “age” (< 65 years versus ≥ 65 years)

Based on the available and evaluable results, overall at outcome level only positive effects remain, each with the same probability (hint). These were shown in the outcome categories “mortality”, “serious/severe symptoms/late complications”, and “serious/severe AEs” and “non-serious/non-severe symptoms/late complications”. For the derivation of the overall conclusion on added benefit, the hint of a major added benefit in terms of overall survival is decisive. Overall, without consideration of the results that showed an indication of an effect modification by the characteristic “age”, there is thus first of all a hint of a major added benefit of enzalutamide + BSC compared with BSC.

For patients < 65 years there was also a hint of a considerable added benefit, and for patients ≥ 65 years a hint of a minor added benefit, in each case for the outcome “time to first skeletal-related complication”. In neither case does this have any effect on the overall result (hint of a major added benefit).

Overall, the characteristic “age” has no influence on the overall conclusion on added benefit.

Summary

In summary, for patients with metastatic castration-resistant prostate cancer with visceral metastases whose disease has progressed during or after docetaxel chemotherapy, there is a hint of a considerable added benefit of enzalutamide + BSC over the ACT (BSC). For patients without visceral metastases, there is a hint of a major added benefit of enzalutamide + BSC over the ACT (BSC).

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The decision on added benefit is made by the G-BA.

2.2 Research question

The aim of the present report was to assess the added benefit of enzalutamide compared with the ACT in the treatment of men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel chemotherapy.

The G-BA specified BSC (e.g. adequate pain therapy) as the ACT, where treatment under BSC is understood as the therapy that ensures the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.

The company followed the specification of the G-BA. The ACT specified by the G-BA was used for this benefit assessment.

Studies that investigated a comparison of enzalutamide with or without BSC versus BSC could be considered for the benefit assessment.

The assessment was conducted based on patient-relevant outcomes and on direct comparative RCTs.

Further information about the research question can be found in Module 3, Section 3.1 and in Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- list of studies on enzalutamide (studies completed up to 1 July 2013)
- bibliographical literature search for studies on enzalutamide (last search on 8 July 2013)
- search in trial registries for studies on enzalutamide (last search on 25 June 2013)

The Institute's own searches to check the completeness of the study pool:

- search in bibliographical databases for studies on enzalutamide (last search on 20 September 2013)
- search in trial registries for studies on enzalutamide (last search on 12 September 2013)

The results of this check produced no deviations from the study pool described in the dossier.

Further information on the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The AFFIRM study listed in Table 2 was included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third party study (yes/no)
AFFIRM	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. BSC: best supportive care; RCT: randomized controlled trial			

Section 1.6 contains a list of data sources for the study included. This study (AFFIRM) was the approval study for enzalutamide.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Characteristics of the studies and the interventions

Table 3 and Table 4 describe the study used for the benefit assessment.

Table 3: Characteristics of the studies included – RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AFFIRM	RCT, double-blind, placebo-controlled, Phase III study, parallel	Men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel chemotherapy	Enzalutamide + BSC (N = 800) Placebo + BSC (N = 399)	Screening: ≤ 28 days before start of study treatment Study treatment: until withdrawal of consent, until occurrence of non-acceptable toxicity, until occurrence of confirmed progression and start of systemic antineoplastic treatment or until death Follow-up for adverse events: up to 30 days after stopping the study medication Long-term follow-up: every 12 weeks until end of study	156 study centres in 15 countries in Australia, Europe, North America, South Africa and South America 9/2009 – 9/2011 (Data cut-off of the interim analysis) The interim analysis after 520 deaths led to the ending of the study.	Primary outcome: overall survival Secondary outcomes: skeletal-related complications, pain, health-related quality of life and adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for this benefit assessment.

BSC: best supportive care; N: number of randomized patients; RCT: randomized controlled trial

Table 4: Characteristics of the interventions – RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study	Intervention	Comparison	Concomitant therapy
AFFIRM	Enzalutamide 160 mg/daily (4 capsules, each of 40 mg)	Placebo 4 capsules daily	The study report only describes which restrictions applied to the concomitant therapies (see the explanations below).
Explanations on the implementation of BSC The following restrictions applied to the concomitant therapies for palliative treatment: In the first 13 weeks after starting the study treatment only one type of long-acting narcotic analgesic, one analgesic for breakthrough pain and one non-steroidal anti-inflammatory drug could be used. The dose and use of other drugs with an effect on pain were specified in the screening period and were also not to be altered in the first 13 weeks after starting the study treatment. Corticosteroids for systemic use could be given up to a daily dose of 10 mg equivalent of prednisone or prednisolone. If a patient was being treated with bisphosphonates at the start of the study, the treatment was to be continued, but the dose was not to be altered during the course of the study. Deviations were only permitted if they were absolutely necessary for the patient's well-being. In the case of deviations, it had to be agreed with the sponsor's medical monitor whether or not the patient was still suitable for the study.			
BSC: best supportive care; RCT: randomized controlled trial			

The AFFIRM study is a randomized, double-blind, placebo-controlled study. It was of a multicentre design and was carried out in Australia, Europe, North and South America as well as South Africa. Men with metastatic castration-resistant prostate cancer, whose disease had progressed on or after docetaxel chemotherapy, were enrolled in the study.

1199 patients were randomized in a ratio of 2:1, 800 in the enzalutamide arm and 399 in the placebo arm. The patients enrolled in the study were considered overall to have met the criteria of the approved therapeutic indication for enzalutamide (see Section 2.7.2.4.1 of the full dossier assessment). This concurs with the company's assessment.

Patients in the enzalutamide arm received 160 mg enzalutamide per day, whilst patients in the placebo arm received placebo. The study treatment with enzalutamide was administered according to a treatment regimen that corresponded to the description in the Summary of Product Characteristics [3].

To enable the AFFIRM study to be evaluated as relevant for the research question of the present benefit assessment, it was necessary to investigate, on the basis of the concomitant therapies, whether the ACT specified by the G-BA (BSC) was implemented adequately in the placebo-controlled study. This investigation produced uncertainties, particularly concerning the pain therapy.

According to the information in the study protocol and in the study report, pain treatment in the first 13 weeks after starting the study treatment was specified as a single, long-acting

narcotic analgesic, a drug to treat breakthrough pain (rescue medication) and, if necessary, a non-steroidal anti-inflammatory agent. Deviations from the specifications regarding the concomitant therapy (and hence also the pain treatment) were only permissible if it was absolutely necessary for the patient's well-being; in this context, continuation of the patient in the study had to be agreed with the company's medical monitor. Based on this information, it is unclear whether an adequate pain therapy was ensured for the patients during this period. In particular with regard to the highly potent analgesics (e.g. World Health Organization [WHO] Step 3) it can be necessary to switch a patient's analgesic because of AEs or lack of efficacy. In view of the high obstacles imposed by the requirements of the study protocol, it is questionable whether such a switch was undertaken by the investigators to an adequate extent and at an adequate point in time. Moreover, it is unclear from the information in the study documents how patients who had not yet received pain therapy at the start of the study were managed. According to the study report (but not, however, according to the study protocol), the analgesics were only specified for those patients who required pain therapy at the screening visit (up to 4 weeks before randomization). Since 83% of patients received at least one analgesic during the study, this applied to at least 17% of patients. Furthermore, it is not clear from the case report form (CRF) how the specification of the pain therapy for the first 13 weeks after starting the study treatment was to be documented. Therefore it is not clear from the study documents how and – if applicable – which analgesics were specified for the patients.

From the concomitant drugs given during the course of the study it is clear that a higher proportion of patients in the placebo arm were treated with highly potent analgesics (WHO Step 3) than in the enzalutamide arm. Although this can be taken as an indication that at some time during the study an individual pain therapy in the sense of a BSC was used, it gives no information about the administration of analgesics in the first 13 weeks after enrolment in the study.

Radiotherapy of the bone was permitted as concomitant therapy. However, this treatment meant that the patient met the criterion of a skeletal-related complication and hence fulfilled the criterion of progression. As mentioned later in this section, progression led to discontinuation of the study treatment if subsequent treatment with a systemic antineoplastic therapy was also planned.

Finally, it should be mentioned that there was no indication in the study documents that the patients were able to receive any palliative treatment according to guidelines.

In particular due to the restrictions in pain therapy in the first 13 weeks, it was therefore unclear whether the ACT was adequately implemented in the AFFIRM study for the present research question. For this reason, the AFFIRM study is subject to an overall increased uncertainty for the research question of the benefit assessment. This was taken into account when deriving added benefit, in that the probability was reduced by one level (e.g. from

"indication" to "hint"). Despite the uncertainty, the treatment in the placebo arm of the study is hereinafter termed "BSC".

The assessment concerning the implementation of the ACT deviates from that of the company, which stated that patients in both arms of the study received, in addition to the therapy enzalutamide or placebo, an individualized supportive treatment according to BSC, e.g. adequate pain therapy (see Section 2.7.2.4.1 of the full dossier assessment).

The study treatment was continued until at least one of the following stopping criteria occurred:

- withdrawal of the patient's consent
- safety concerns (e.g. non-acceptable toxicity)
- occurrence of progression (bone metastases, soft tissue metastases or skeletal-related complication) and subsequent treatment with a systemic antineoplastic therapy

After the end of study treatment, patients first underwent a follow-up of up to 30 days to record AEs and then a long-term follow-up every 12 weeks until the end of the study. The primary outcome was overall survival.

An interim analysis of the study after 520 deaths and a final analysis after 650 deaths were originally planned. The interim analysis was conducted after 520 deaths as intended and, because of the efficacy results, the recording of data was then stopped for all outcomes except overall survival and pharmacovigilance, which is why the originally planned final analysis was not undertaken. The company submitted the results on overall survival for 3 further data cut-offs to the regulatory authorities. For these 3 data cut-offs, there was no information on the treatment of patients at the time of the data cut-off. It was therefore unclear how many patients at the time of the data cut-offs were still under the randomized treatment. The influence of treatments at the time of the data cut-offs on overall survival cannot be assessed. The results on the 3 data cut-offs are therefore subject to increased uncertainty. The results on overall survival from the 3 further data cut-offs are shown additionally. This deviates from the company's approach, which did not show the 3 further data cut-offs in Module 4.

All outcomes were recorded up to the end of study treatment. The visits thereafter took place 30 days after the last dose of study medication and data on AEs, concomitant drugs and the Eastern Cooperative Oncology Group Performance Status (ECOG PS) were documented. These visits were brought forward if the patient was given a systemic antineoplastic follow-up therapy (e.g. chemotherapy). During the long-term follow-up, data were collected on overall survival, on subsequent antineoplastic treatments of the prostate cancer, on the time to first skeletal-related complication, and on radiographic progression.

The patients of both treatment arms were followed up for overall survival for a median of 14.4 months, whilst the median follow-up time for AEs was 9.3 months in the enzalutamide arm

and 3.8 months in the placebo arm. The median treatment duration with the study medication was 8.3 months in the enzalutamide arm and 3.0 months in the placebo arm.

Characteristics of the study populations

Table 5 shows the characteristics of the patients in the study included in the assessment.

Table 5: Characteristics of the study populations – RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study Characteristics Category	**Enzalutamide + BSC (N = 800)**	**Placebo/BSC (N = 399)**
AFFIRM		
Age [years] mean (SD)	69 (8.0)	69 (8.4)
ECOG Performance Status at start of study, n (%)		
0	298 (37.3)	156 (39.1)
1	432 (54.0)	211 (52.9)
2	70 (8.8)	32 (8.0)
Average pain score of the BPI-SF (Question 3)[a], n (%)		
< 4	574 (71.8)	284 (71.2)
≥ 4	226 (28.3)	115 (28.8)
Duration of the disease: time between first diagnosis and randomization [months], mean (SD)	86 (54.8)	82 (50.9)
Site of metastasis, n (%) at start of study		
Bone	225 (28.1)	123 (30.8)
Soft tissue	62 (7.8)	34 (8.5)
Bone and soft tissue	505 (63.1)	241 (60.4)
None	8 (1.0)	1 (0.3)
Number of previous chemotherapies, n (%)		
1	579 (72.4)	296 (74.2)
2	196 (24.5)	95 (23.8)
≥ 3	25 (3.1)	8 (2.0)
Number of study discontinuations, n (%)	569 (71.1[b])	380 (95.2[b])

a: Assessment of the worst pain within the last 24 hours on an 11-point scale of 0 (no pain) to 10 (worst pain imaginable).
b: Institute's calculation.
BPI-SF: Brief Pain Inventory – Short Form; BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; N: number of randomized patients; n: number of patients in category; RCT: randomized controlled trial; SD: standard deviation.

Patient characteristics were largely comparable in both treatment arms. The average age of the study population was 69 years; about 92% of patients had an ECOG-PS of 0 or 1, and only about 8% of patients had an ECOG-PS of 2. Patients with an ECOG-PS > 2 were excluded from the study. At the start of the study about 71% of patients had a Brief Pain Inventory – Short Form (BPI-SF) pain score of < 4 and about 29% a score of ≥ 4. The mean duration of

the disease was 86 months in the enzalutamide arm and 82 months in the placebo arm. More than 99% of patients had metastases at enrolment in the study; 505 (63.1%) of patients in the enzalutamide arm and 241 (60.4%) of patients in the placebo arm had metastases in the bones and soft tissue. All patients had been previously treated with docetaxel. In about 73% of patients this was the only chemotherapy, whereas about 24% of patients had been previously treated with 2 chemotherapies and about 3% of patients with ≥ 3 chemotherapies.

Table 6 shows the risk of bias at study level.

Table 6: Risk of bias at study level – RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study	Adequate randomization sequence generation	Allocation concealment	Blinding		No selective reporting	No other aspects	Risk of bias at study level
			Patient	Treating staff			
AFFIRM	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial							

The risk of bias at study level for the AFFIRM study was rated as low. This concurs with the company's assessment.

Further information about study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and in Appendix 4-G of the dossier as well as in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

Outcomes considered

The following patient-relevant outcomes were included in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - time to first skeletal-related complication
  - time to pain progression
  - change in pain intensity
  - paralyses and paralysis-related urinary incontinence

- Health-related quality of life
  - Functional Assessment of Cancer Therapy – Prostate (FACT-P)
  - European Quality of Life-5 Dimensions (EQ-5D)
- Adverse events
  - severe AEs (CTCAE Grade ≥ 3)
  - SAEs
  - treatment discontinuations due to AEs
  - seizures

The Institute's choice of patient-relevant outcomes differed from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 7 shows for which outcomes data were available in the study included.

Table 7: Matrix of outcomes – RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study	Outcomes										
	Overall survival	**Time to first skeletal-related complication**	**Health-related quality of life according to FACT-P**	**Health-related quality of life according to EQ-5D**	**Time to pain progression**	**Change in pain intensity**	**Paralyses and paralysis-related urinary incontinence**	**Serious adverse events**	**Treatment discontinuation due to adverse event**	**Severe adverse event (CTCAE Grade ≥ 3)**	**Seizures**
AFFIRM	Yes	Yes	No[a]	No[a]	Yes	Yes	No[a]	Yes[b]	Yes[b]	Yes[b]	No[a]

a: No evaluable results in dossier of the company; for reasons, see Sections 2.7.2.2 and 2.7.2.4.3 of the of the full dossier assessment.
b: As described in Section 2.7.2.4.2 of the full dossier assessment, the outcomes could only be qualitatively interpreted.
BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; RCT: randomized controlled trial

Risk of bias

Table 8 describes the risk of bias for the outcomes included.

Table 8: Risk of bias at study and outcome level – RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study	Study level	Outcomes										
		Overall survival	Time to first skeletal-related complication	Health-related quality of life according to FACT-P	Health-related quality of life according to EQ-5D	Time to pain progression	Change in pain intensity	Paralyses and paralysis-related urinary incontinence	Serious adverse events	Treatment discontinuation due to adverse event	Severe adverse events (CTCAE-Grade ≥ 3)	Seizures
AFFIRM	L	L	L	-[a]	-[a]	L	H	-[a]	-[b]	-[b]	-[b]	-[a]

a: No evaluable data available.
b: Results only interpretable in qualitative terms.
BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; H: high; L: low; RCT: randomized controlled trial

The dossier contained no evaluable data on health-related quality of life (FACT-P and EQ-5D), on paralyses and paralysis-related urinary incontinence or on seizures. Therefore no outcome-specific assessment of the risk of bias was conducted.

The risk of bias for the outcomes "overall survival", "time to first skeletal-related complication" and "time to pain progression" was rated as low. This concurs with the company's assessment. The risk of bias of the continuous analysis for the outcome "change in pain intensity" was rated as high. This assessment concurs with that of the company, which submitted the analysis of the continuous data on Question 3 of the BPI-SF as an additional analysis under the outcome "rate of pain progression".

The results on the outcomes "SAEs", "treatment discontinuation due to AEs" and "severe AEs (CTCAE Grade ≥ 3)" could only be interpreted in qualitative terms. In Module 4 of the dossier, the company presented solely analyses on the basis of the naive proportions of patients with at least one event. Because of the marked differences in treatment duration of patients in the 2 treatment arms (median 8.3 months in the enzalutamide arm and 3.0 months in the placebo arm) and the marked differences in observation period for AEs in the 2 treatment arms (median 9.3 months in the enzalutamide arm and 3.8 months in the placebo arm), these analyses were only evaluable for the benefit assessment to a limited extent. Due to the differences in treatment duration and observation period, more SAEs, treatment discontinuations due to AEs and severe AEs (CTCAE Grade ≥ 3) could occur in the

enzalutamide arm than in the placebo arm. There was thus a bias to the disadvantage of enzalutamide. This assessment deviated from that of the company, which considered the risk of bias for these outcomes as low.

The interpretation of the results depends on the direction of effect observed. In the case of statistically significant differences in favour of enzalutamide + BSC, due to the known direction of bias to the disadvantage of enzalutamide + BSC, a conclusion can, however, be derived that a greater harm of enzalutamide is excluded. Furthermore, it is assumed that the statistically significant effect in favour of enzalutamide + BSC would remain on resolution of the bias. In the case of statistically non-significant differences, the only conclusion to be derived is that, despite the bias to the disadvantage of enzalutamide, the submitted data showed no greater harm. A statistically significant effect to the disadvantage of enzalutamide was not observed.

Moreover, when interpreting the adverse events, it should be borne in mind that some of the AEs in the AFFIRM study represent aspects of benefit (e.g. fatigue or pain). This means that patients with events were also included who might have been included at the same time through specifically recorded outcomes on morbidity (e.g. pain progression). Provided that enzalutamide + BSC has a higher benefit than BSC alone, it is possible that the proportion of patients with AEs due to aspects of benefit is higher in the placebo arm than in the enzalutamide arm, which led to a potential bias of the results in favour of enzalutamide. A check of the events that had occurred was therefore carried out to see whether the results on AEs were substantially affected by those AEs explained by the aspects of benefit. However, the influence of these events was regarded as not so high as to mask a possible disadvantage of enzalutamide in terms of the considered outcomes on AEs.

The assessment of the risk of bias is justified in Section 2.7.2.4.2.

Further information about the choice of outcome and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2 and, 2.7.2.4.3 of the full dossier assessment.

Presentation of the results

Table 9, Table 10 and Table 11 summarize the results on the comparison of enzalutamide + BSC with BSC in patients in the therapeutic indication. Where necessary, the data from the company's dossier were supplemented by the Institute's own calculations. The Kaplan-Meier curves for the outcomes "overall survival", "time to first skeletal-related complication" and "time to pain progression" can be found in Appendix B of the full dossier assessment.

Table 9 shows the results on overall survival for 3 further data cut-offs in addition to the results of the interim analysis presented by the company in Module 4. These 3 data cut-offs were generated after the data collection was halted and relate only to overall survival. The first data cut-off after the interim analysis occurred at the time of the database closure (16 December 2011) and was reported in the study report as an additional analysis. The 2

other data cut-offs (31 January 2102 and 29 June 2012) took place at the same time as the data cut-offs to produce reports for the regulatory authorities as part of the pharmacovigilance process. The results of the last 2 data cut-offs can be found in the Day 150 Report of the European Medicines Agency [4]. No information about the treatment at the time of the data cut-off was available for the 3 data cut-offs after the interim analysis. It was therefore unclear how many patients were still undergoing randomized treatment at the time of the data cut-offs. The influence of treatments at the time of the data cut-offs on overall survival cannot be assessed. The results of the 3 data cut-offs are therefore subject to increased uncertainty. As a consequence, only the results of the interim analysis (data cut-off 25 November 2011) were taken into account when deriving the extent of added benefit.

The analysis that was used for interpreting the outcome “treatment discontinuation due to AEs” was the one that considered all patients who had at least one AE which led to the discontinuation of the study medication (named in the CRF as “AEs with the action treatment discontinuation”). This deviates from the company’s approach, which, in Module 4, showed the analysis of only those patients for whom AEs were named as the primary reason for treatment discontinuation (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).

Table 9: Results (overall survival and morbidity) – RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study Outcome	Enzalutamide + BSC		Placebo + BSC		Enzalutamide + BSC vs. placebo + BSC
	N	Median time to event in months [95% CI]	N	Median time to event in months [95% CI]	HR [95% CI]; p-value
AFFIRM					
Overall survival **Data cut-off**					
25 September 2011 (primary analysis)	800	18.4 [17.3; n.r.]	399	13.6 [11.3; 15.8]	0.63 [0.53; 0.75]; p < 0.001[a]
16 December 2011	800	17.8 [16.7; 18.8]	399	13.3 [11.2; 14.2]	0.62 [0.52; 0.73]; p < 0.001[b]
31 January 2012[c]	800	18.3 [n.d.]	399	13.5 [n.d.]	0.67 [0.57; 0.79]; p < 0.001[b]
29 June 2012[c]	800	18.4 [n.d.]	399	13.5 [n.d.]	0.70 [0.60; 0.81]; p < 0.001[b]
Morbidity					
Time to first skeletal-related complication	800	16.7 [14.6; 19.1]	399	13.3 [9.9; n.r.]	0.69 [0.57; 0.84]; p < 0.001[a]
Time to radiation of bone	800	n.r. [18.7; n.r.]	399	n.r. [18.2; n.r.]	0.71 [0.55; 0.91]; p = 0.006
Time to bone surgery	800	n.r. [n.r.]	399	n.r. [n.r.]	2.49 [0.30; 20.79]; p = 0.38
Time to pathological bone fracture	800	n.r. [n.r.]	399	n.r. [n.r.]	0.85 [0.47; 1.56]; p = 0.60
Time to spinal cord compression	800	21.6 [21.6; n.r.]	399	n.r. [n.r.]	1.00 [0.64; 1.55]; p = 0.99
Time to change of antineoplastic therapy to treat bone pain	800	n.r. [n.r.]	399	n.r. [n.r.]	0.54 [0.28; 1.04] p = 0.06
Time to pain progression[d]	800	11.0 [8.2; 13.8][e]	399	4.6 [3.7; 5.5][e]	0.56 [0.41; 0.78]; p < 0.001[a]

a: The p-value from the log-rank test was adjusted according to ECOG and BPI-SF (Question 3).
b: Institute's calculation.
c: Data from Day 150 Assessment Report of the regulatory authorities [4].
d: Recorded from the following item from FACT-P: "I have pain", which the patients answered using a 5-point scale from 0 to 4 points (0 = no pain to 4 = very much pain).
e: The 25% quartile is shown, i.e. the time at which 25% of the patients had an event (Kaplan-Meier estimate). The median time to the event and the associated CI could not be estimated because at the time of analysis less than 50% of patients in the enzalutamide arm had had an event.

BPI-SF: Brief Pain Inventory – Short Form; BSC: best supportive care; CI: confidence interval;
ECOG: Eastern Cooperative Oncology Group; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HR: hazard ratio; N: number of analysed patients; n.d.: no data; n.r.: not reached; RCT: randomized controlled trial; vs.: versus

Table 10: Results (morbidity and health-related quality of life) – RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study Outcome category Outcome	Enzalutamide + BSC			Placebo + BSC			Enzalutamide + BSC vs. placebo + BSC
	N	Values at start of study mean (SD)	Change at study end mean (SD)	N	Values at start of study mean (SD)	Change at study end mean (SD)	SMD[a] [95% CI]; p-value
AFFIRM							
Morbidity							
Change in pain intensity[b]	620	2.4 (2.2)	-0.4 (2.0)	259	2.2 (2.2)	0.6 (2.2)	-0.48 [-0.62; -0.34]; p < 0.001
Paralyses and paralysis-related urinary incontinence	No evaluable results						
Health-related quality of life							
FACT-P	No evaluable results						
EQ-5D	No evaluable results						

a: Effect estimate not further defined.
b: Only recorded at start of study and Week 13. The data of Question 3 of the BPI-SF were analysed: Assessment of the worst pain within the last 24 hours on an 11-point scale from 0 (no pain) to 10 (worst pain imaginable).

BPI-SF: Brief Pain Inventory – Short Form; BSC: best supportive care; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference; vs.: versus

Table 11: Results (adverse events) – RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study Outcome category Outcome	Enzalutamide + BSC	Placebo + BSC	Enzalutamide + BSC vs. placebo + BSC
AFFIRM			
Adverse events			
Treatment discontinuation due to AEs	Results only interpretable in qualitative terms[a]		
Severe AEs (CTCAE Grade ≥ 3)	Results only interpretable in qualitative terms[a]		
SAEs	Results only interpretable in qualitative terms[a]		
Seizures	No evaluable results		

a: See Appendix A, Table 21 of the full dossier assessment for the presentation of the naive proportions of patients with events

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The particular requirements for derivation of proof from a single study are not met by the AFFIRM study (see Section 2.7.2.8.1 of the full dossier assessment). Furthermore, the certainty of results of the study was downgraded by one further level, because it is only partially clear whether the study answers the research question (determination of added benefit of enzalutamide compared with BSC) (see Section 1.3.2). Hence, the maximum that can be inferred from the data are hints, for instance of an added benefit. This deviates from the company's assessment, which maintained that the AFFIRM study is suitable for deriving proof.

Mortality

Overall survival

In all 4 data cut-offs the treatment with enzalutamide + BSC produced a statistically significant prolongation in overall survival compared with placebo + BSC. Based on the total population of the AFFIRM study, this provides a hint of added benefit of enzalutamide + BSC compared with BSC for the outcome "overall survival".

In addition, there was an indication of an effect modification for the outcome "overall survival" by the characteristic "visceral metastases at the time of screening" (interaction test: $p = 0.15$). It was therefore also necessary to consider the results for patients with or without visceral metastases separately. The subgroup analyses provide a hint of added benefit of enzalutamide + BSC compared with BSC for patients without visceral metastases, but not, however, for patients with visceral metastases (see below).

This assessment deviates from that of the company which on the basis of the total population, derived proof of added benefit for this outcome and did not consider the subgroups.

Morbidity

Time to first skeletal-related complication

The time to first skeletal-related complication was statistically significantly longer under treatment with enzalutamide + BSC than under treatment with placebo + BSC. This provides a hint of added benefit of enzalutamide + BSC compared with BSC for the outcome "time to first skeletal-related complication".

In addition, for this outcome there was an indication of an effect modification by the characteristic "age" (interaction test: $p = 0.199$). It was therefore also necessary to consider the results for patients < 65 years and ≥ 65 years separately. In both age subgroups there is a hint of an added benefit of enzalutamide + BSC compared with BSC for the outcome "time to first skeletal-related complication" (see below).

This assessment deviates from that of the company which, on the basis of the total population of the AFFIRM study, derived proof of added benefit for this outcome and did not consider the subgroups.

Time to pain progression

The time to pain progression was recorded on the basis of an item from the FACT-P ("I have pain"), which was answered by the patients using a 5-point scale from 0 to 4 points (0 = no pain to 4 = very much pain). A deterioration of at least 1 point compared with the start of the study was rated as pain progression.

The time to pain progression was statistically significantly longer under treatment with enzalutamide + BSC than under treatment with placebo + BSC. This provides a hint of an added benefit of enzalutamide + BSC compared with BSC for the outcome "time to pain progression".

This assessment deviates from that of the company, which derived proof of added benefit for this outcome.

Change in pain intensity

The change in pain intensity was recorded on the basis of Question 3 of the BPI-SF that comprises an assessment of the worst pain within the last 24 hours on an 11-point scale from 0 (no pain) to 10 (worst pain imaginable).

On the basis of the continuous data on the change in pain intensity, treatment with enzalutamide + BSC produced statistically significantly less pain than the treatment with placebo + BSC. Since no scale-specific validated or established relevance criteria for the group difference and also no evaluable responder analyses were available, the standardized mean difference (SMD) was used for assessing relevance. The upper limit of the 95% confidence interval of the SMD was fully below the irrelevance threshold of −0.2. It could therefore be excluded that the effect for pain was in a certainly irrelevant region. There was a high risk of bias for this outcome. Overall, this therefore provides a hint of an added benefit of enzalutamide + BSC compared with BSC for the outcome "change in pain intensity".

This assessment deviates from that of the company which, on the basis of the responder analysis, derived an indication of added benefit for this outcome.

Paralyses and paralysis-related urinary incontinence

The company's dossier contains no evaluable data on paralyses and paralysis-related urinary incontinence. An added benefit of enzalutamide + BSC compared with BSC in terms of the outcome "paralyses and paralysis-related urinary incontinence" is therefore not proven.

This assessment deviates from that of the company, which did not take into account the results from the descriptive analysis when deriving the added benefit.

Health-related quality of life

Since the company's dossier contained no evaluable data on health-related quality of life, an added benefit of enzalutamide + BSC compared with BSC in terms of the outcome "health-related quality of life" is not proven.

This assessment concurs with that of the company for health-related quality of life according to EQ-5D, but not for health-related quality of life according to FACT-P, where the company derived an indication of an added benefit.

Adverse events

SAEs, treatment discontinuation due to AEs and severe AEs (CTCAE Grade ≥ 3)

Module 4 of the dossier contains no valid analyses for the assessment of adverse events that could be included in the benefit assessment. The data submitted by the company on the basis of naive proportions (proportion of patients with at least one event) do not constitute an adequate analysis because of the marked differences in treatment duration and observation period of the patients in the 2 treatment arms (observation period: 9.3 months in the enzalutamide arm and 3.8 months in the placebo arm). The company's analyses of the number of events per 100 patient years (based on the observation period) shown in Module 5 could not be considered (see Section 2.7.2.4.2 of the full dossier assessment).

As regards severe AEs (CTCAE Grade ≥ 3), a statistically significant difference in favour of enzalutamide + BSC was shown on the basis of naive proportions. Under consideration of the known direction of bias, it can be qualitatively derived from these results that a greater harm of enzalutamide + BSC compared with BSC is ruled out. It is also to be assumed that the statistically significant effect in favour of enzalutamide + BSC would persist on resolution of the bias. This provides a hint of lesser harm of enzalutamide + BSC compared with BSC for the outcome "severe AEs" (CTCAE Grade ≥ 3).

As regards the outcomes "SAEs" and "treatment discontinuation due to AEs", no statistically significant difference between the treatment arms was shown on the basis of the naive proportions. In these cases, the only derivable conclusion is that, despite the bias to the disadvantage of enzalutamide in the submitted data, no greater harm was shown. Hence, greater or lesser harm of enzalutamide + BSC compared with BSC for SAEs and treatment discontinuation due to AEs is not proven.

The assessment that greater or lesser harm of enzalutamide + BSC compared with BSC is not proven for the outcomes "SAEs" and "treatment discontinuations due to AEs" concurs with that of the company. For the outcome "severe AEs" (CTCAE Grade ≥ 3), it deviates from that of the company, which derived proof of added benefit.

Seizures

No evaluable results were available for seizures, because it is unclear whether the results presented by the company reflect this outcome with adequate reliability. Greater or lesser harm of enzalutamide + BSC compared with BSC is not proven for this outcome.

This assessment concurs with that of the company, which reported seizures only in descriptive terms and did not include them when deriving the added benefit.

Subgroup analyses

In order to uncover possible effect differences between patient groups, the following potential effect modifiers were included: ECOG-PS at the start of the study (0 or 1 versus 2), average pain score of the BPI-SF (Question 3) at the start of the study (< 4 versus ≥ 4), age (< 65 versus ≥ 65), geographical region (North America versus Europe versus the rest of the world), number of previous chemotherapies (1 versus ≥ 2) and visceral metastases (lungs and/or liver) at the time of screening (yes versus no). With the exception of the geographical region, a possible effect modification was investigated for all outcomes. The subgroup analyses for the potential effect modifier "geographical region" could only be carried out for overall survival.

The prerequisite for proof of differing effects is a statistically significant homogeneity and/or interaction test ($p \leq 0.05$). A p-value between 0.05 and 0.2 provided an indication of different effects. The interaction tests were available from the dossier. There was no proof ($p < 0.05$) of an effect modification from any of the subgroup analyses.

Table 12 and Table 13 show the results of the subgroup analyses for subgroup characteristics for which an indication of an effect modification was provided.

Table 12: Subgroups with indications of interaction (overall survival and time to first skeletal-related complication): RCT, direct comparison: enzalutamide + BSC versus placebo + BSC

Study **Outcome** **Characteristic** **Subgroup**	**Enzalutamide + BSC**		**Placebo + BSC**		**Enzalutamide + BSC vs. placebo + BSC**	
	N	**Median time to event in months [95% CI]**	N	**Median time to event in months [95% CI]**	**HR [95% CI]**	**p-value**
AFFIRM						
Mortality						
Overall survival						
Visceral metastases at time of screening						
Yes	196	13.4 [10.4; 16.5]	82	9.5 [6.9; 15.5]	0.78 [0.56; 1.09]	0.148
No	604	n.r. [18.3; n.r.]	317	14.2 [12.4; 17.6]	0.57 [0.46; 0.70]	< 0.001
					Interaction:	0.15
Morbidity						
Time to first skeletal-related complication						
Age						
< 65	232	14.4 [11.8; 17.7]	130	8.6 [4.1; 13.3]	0.60 [0.44; 0.83]	0.002
≥ 65	568	18.7 [15.3; n.r.]	269	15.0 [12.1; n.r.]	0.77 [0.60; 0.99]	0.04
					Interaction:	0.199

BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n.r.: not reached; RCT: randomized controlled trial

Table 13: Subgroups with indications of interaction (change in pain intensity): RCT, direct comparison: enzalutamide + BSC vs. placebo + BSC

Study Outcome Characteristic Subgroup	Enzalutamide + BSC			Placebo + BSC			Enzalutamide + BSC vs. placebo + BSC
	N	Values at start of study mean (SD)	Change at Week 13 mean (SD)	N	Values at start of study mean (SD)	Change at Week 13 mean (SD)	SMD[a] [95% CI]; p-value
AFFIRM							
Morbidity							
Change in pain intensity[b]							
ECOG-PS at start of study							
≤ 1	576	2.25 (2.04)	-0.29 (1.94)	242	2.10 (2.04)	0.64 (2.16)	-0.46 [-0.61; -0.31]; p < 0.001
2	44	4.46 (2.47)	-1.18 (2.79)	17	3.96 (2.90)	0.64 (2.31)	-0.68 [-1.22; -0.14]; p = 0.02
						Interaction:	p = 0.14
Average pain score of BPI-SF (Question 3[b]) at start of study							
< 4	467	1.40 (1.23)	0.13 (1.64)	203	1.33 (1.32)	0.95 (1.99)	-0.46 [-0.62; -0.30]; p < 0.001
≥ 4	153	5.50 (1.20)	-1.83 (2.34)	56	5.46 (1.31)	-0.47 (2.40)	-0.58 [-0.88; -0.28]; p < 0.001
						Interaction:	p = 0.10

a: Effect estimate not further defined.
b: Question 3 of the BPI-SF comprises the assessment of the worst pain within the last 24 hours on an 11-point scale from 0 (no pain) to 10 (worst pain imaginable).
BPI-SF: Brief Pain Inventory – Short Form; BSC: best supportive care; CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference

Mortality

Overall survival

For overall survival, there was an indication of an effect modification by the subgroup characteristic "visceral metastases".

For the patients without visceral metastases, treatment with enzalutamide + BSC produced a statistically significant prolongation in overall survival compared with placebo + BSC. This provides a hint of added benefit of enzalutamide + BSC compared with BSC for patients without visceral metastases for the outcome "overall survival".

There was no statistically significant difference in terms of the duration of overall survival for the patients with visceral metastases. Hence, an added benefit for the subgroup of patients with visceral metastases is not proven for the outcome "overall survival". The following aspects need to be considered in this derivation: since merely an indication of an effect

modification by the metastases status was present, the statistically significant result for overall survival in the total population should be borne in mind when interpreting the results for this subgroup. Due to the lack of a statistically significant effect in the subgroup, there is however, an increased uncertainty. As the AFFIRM study is basically only suitable for deriving hints (for reasons, see Section 1.3.2 as well as Section 2.7.2.8.1 of the full dossier assessment), the additional uncertainty from the subgroup analysis means that in the present case, an added benefit for the subgroup of patients with visceral metastases is not proven for the outcome "overall survival".

These assessments deviate from those of the company, which, although it described the indication of the effect modification by visceral metastases when deriving the added benefit, did not take this into account, as it derived the proof of added benefit exclusively on the basis of the total population.

Morbidity

Time to first skeletal-related complication

There was an indication of an effect modification by age (< 65 years or ≥ 65 years) for the time to first skeletal-related complication.

Treatment with enzalutamide + BSC produced a statistically significant prolongation in the time to first skeletal-related complication compared with placebo + BSC, both for the patients < 65 years and also for the patients ≥ 65 years. This provides a hint of an added benefit of enzalutamide + BSC compared with BSC for both subgroups for the outcome "time to first skeletal-related complication".

These assessments deviate from those of the company which, although it showed the indication of the effect modification by age in the results section of Module 4, did not take this into account when deriving the added benefit. It derived proof of added benefit exclusively on the basis of the total population.

Change in pain intensity

For the outcome "change in pain intensity" there was an indication of an effect modification by the characteristics "ECOG-PS at the start of the study" and "pain score at the start of the study" respectively.

In each of the respective subgroups there was a statistically significant difference in favour of enzalutamide. The size of the subgroups differed considerably for both characteristics. In addition, the 95% confidence interval for the group difference of the larger subgroup in each case (e.g. patients with ECOG-PS ≤ 1) was completely within the confidence interval of the respective other subgroup. These subgroup analyses could therefore only be interpreted to a limited extent and are not considered further in the following text.

Further information about choice of outcome, risk of bias at outcome level and outcome results can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit at outcome level is presented below, taking into account the various outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The decision on added benefit is made by the G-BA.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 1.4 showed indications of effect modifications for the subgroup characteristics age (< 65, ≥ 65) and visceral metastases (yes versus no) at the start of the study. The extent of the respective added benefit at outcome level was estimated from these results (see Table 14). In the overall assessment, it was then investigated whether different conclusions on the extent of added benefit arise for the individual patient groups.

Table 14: Extent of added benefit at outcome level: enzalutamide + BSC versus BSC

Outcome category **Outcome** Effect modifier Subgroup	**Enzalutamide + BSC vs. placebo + BSC** **Median time to event or proportion of events or MD**[a] **Effect estimate [95% CI]** **p-value** **Probability**[b]	**Derivation of extent**[c]
Mortality		
Overall survival	Median: 18.4 vs. 13.6 months HR: 0.63 [0.53; 0.75] p < 0.001 Probability: "hint"	Outcome category: survival period $CI_u < 0.85$ Added benefit, extent "major" [d]
Visceral metastases		
Yes	Median: 13.4 vs. 9.5 months HR: 0.78 [0.56; 1.09] p = 0.148	Lesser benefit/added benefit not proven.
No	Median: n.r. vs. 14.2 months HR: 0.57 [0.46; 0.70] p < 0.001 Probability: "hint"	Outcome category: survival period $CI_u < 0.85$ Added benefit, extent: "major"
Morbidity		
Time to first skeletal-related complication	Median: 16.7 vs.13.3 months HR: 0.69 [0.57; 0.84] p < 0.001 Probability: "hint"	Outcome category: "serious/severe symptoms/late complications" $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"[d]
Age (years)		
< 65	Median: 14.4 vs. 8.6 months HR: 0.60 [0.44; 0.83] p = 0.002 Probability: "hint"	Outcome category: "serious/severe symptoms/late complications" $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
≥ 65	Median: 18.7 vs. 15.0 months HR: 0.77 [0.60; 0.99] p = 0.04 Probability: "hint"	Outcome category: "serious/severe symptoms/late complications" $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Time to pain progression[e]	25% quantile[f]: 11.0. vs. 4.6 months HR: 0.56 [0.41; 0.78] p < 0.001 Probability: "hint"	Outcome category: "non-serious/non-severe symptoms/late complications"[g] $CI_u < 0.80$ Added benefit, extent: "considerable"

(continued)

Table 14: Extent of added benefit at outcome level: enzalutamide + BSC versus BSC (continued)

Outcome category **Outcome** Effect modifier Subgroup	**Enzalutamide + BSC vs. placebo + BSC** **Median time to event or proportion of events or MD**[a] **Effect estimate** [**95% CI]** **p-value** **Probability**[b]	**Derivation of extent**[c]
Morbidity (continuation)		
Change in pain intensity[h]	MD: -0.99 [-1.29; -0.69] SMD: -0.48 [-0.62; -0.34][i] Probability: "hint"	Outcome category: "non-serious/non-severe symptoms/late complications"[j] Added benefit, extent: "non-quantifiable".
Paralyses and paralysis-relate urinary incontinence	No evaluable results available	Lesser benefit/added benefit not proven.
Health-related quality of life		
FACT-P	No evaluable results available	Lesser benefit/added benefit not proven.
EQ-5D	No evaluable results available	Lesser benefit/added benefit not proven.
Adverse events		
SAEs	Qualitative interpretation on the basis of the naive proportions of patients with AEs[k]	Greater/lesser harm not proven.
Treatment discontinuation due to AEs	Qualitative interpretation on the basis of the naive proportions of patients with AEs[k]	Greater/lesser harm not proven.
Severe AEs (CTCAE Grade ≥ 3)	Qualitative interpretation on the basis of the naive proportions of patients with AEs[k] Probability: "hint"	Outcome category serious/severe adverse events Lesser harm, extent: "non- quantifiable"
Seizures	No evaluable results available	Greater/lesser harm not proven.

(continued)

Table 14: Extent of added benefit at outcome level: enzalutamide + BSC versus BSC (continued)

a: Mean difference Week 13 minus baseline value.
b: Probability provided, if statistically significant differences were present.
c: Estimations of effect size are made depending on outcome category with different limits based on the upper limit of the confidence interval (CI_0).
d: Despite the indication of effect modification, the results for the total population are shown because they are relevant in the derivation of added benefit in respect of the subgroup characteristics "age" and presence of "visceral metastases" (see Section 1.5.2).
e: Recorded on the basis of the following question in FACT-P: "I have pain", that was answered by patients using a 5-point scale from 0 to 4 points (0 = no pain to 4 = very much pain).
f: The 25% quantile is the time at which 25% of the patients have an event (Kaplan-Meier estimate). The median time to the event or the associated CI could not be estimated, because at the analysis time point less than 50% of patients in the enzalutamide arm had had an event.
g: The outcome category ("non-serious/non-severe symptoms/late complications") was determined on the basis of the change in pain intensity. This assessment concurs with that of the company.
h: Recorded with Question 3 of the BPI-SF: estimation of the worst pain within the last 24 hours on an 11-point scale from 0 (no pain) to 10 (worst pain imaginable).
i: Standardized effect without definition of the standardization.
j: The outcome category ("non-serious/non-severe symptoms/late complications") was determined from the mean pain score at Week 13. This assessment concurs with that of the company.
k: The naive proportions of patients with events are shown in Appendix A, Table 22 of the full dossier assessment.
AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; BSC: best supportive care; CI: confidence interval; CI_0: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HR: hazard ratio; MD: mean difference; n.r.: not reached; SMD: standardized mean difference; SAE: serious adverse event; vs.: versus

The results showed that for the characteristic "visceral metastases" a relevant effect modification was present for the outcome "overall survival". The same applied to the characteristic "age" for the outcome "time to first skeletal-related complication". In both cases, consideration of the individual subgroups produced a different extent of added benefit at outcome level. Both for patients with and without visceral metastases as well as for the 2 age groups, separate conclusions on added benefit are therefore necessary.

2.5.2 Overall conclusion on added benefit

The derivation of the overall conclusion on added benefit is shown below separately for the 2 relevant subgroup characteristics "visceral metastases" and "age".

2.5.2.1 Subgroup characteristic "visceral metastases"

The summary of results that determine the overall conclusion on added benefit is shown in Table 15. The subgroup effects by the characteristic "visceral metastases" were initially disregarded, in that only those effects were shown in which no indication or proof of an effect modification by the characteristic "visceral metastases" was provided. Thereafter, it was investigated whether different conclusions for patients with or without visceral metastases arose if the results on overall survival were taken into account.

Table 15: Positive and negative effects from the assessment of enzalutamide + BSC compared with BSC on the basis of outcomes in which there was no effect modification by the characteristic "visceral metastases"

Positive effects	**Negative effects**
Hint of an added benefit – extent: "considerable" (serious late complications: time to first skeletal-related complication)	—
Hint of an added benefit – extent: "considerable" (non-serious/non-severe symptoms: time to pain progression)	
Hint of an added benefit – extent: "non-quantifiable" (non-serious/non-severe symptoms: change in pain intensity)	
Hint of lesser harm – extent: "non-quantifiable" (serious/severe AEs: severe AEs [CTCAE Grade ≥ 3])	
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events	

Based on the available and evaluable results, overall only positive effects remain at outcome level, each with the same probability (hint). These were shown in the outcome categories "mortality", "serious/severe symptoms/late complications", "serious/severe AEs" and "non-serious/non-severe symptoms/late complications". For the outcomes "time to first skeletal-related complication" and "time to pain progression", the extent is, in each case, considerable. The extent of added benefit for the outcomes "change in pain intensity" and "severe AEs" is non-quantifiable. The extent category "non-quantifiable" is an expression of the uncertainty regarding the effect size and can also include the extent category "major". However, in the present case, due to the respective effect sizes, it cannot be assumed that the threshold for the extent category "major" is reached. Overall, without consideration of the results that showed an indication of an effect modification by the characteristic "visceral metastases", there is first of all a hint of a considerable added benefit of enzalutamide + BSC compared with BSC.

For patients with visceral metastases, no additional positive or negative effects were shown, so that the overall conclusion (hint of a considerable added benefit) does not change for these patients. For patients without visceral metastases, there is also a hint of a considerable added benefit for the outcome "overall survival". This also changes the overall conclusion on added benefit for these patients to a hint of a major added benefit.

In summary, for patients with metastatic castration-resistant prostate cancer and visceral metastases, whose disease has progressed on or after docetaxel chemotherapy, there is a hint of a considerable added benefit of enzalutamide + BSC compared with the ACT (BSC). For patients with metastatic castration-resistant prostate cancer without visceral metastases, whose disease has progressed on or after docetaxel chemotherapy, there is a hint of a major added benefit of enzalutamide + BSC compared with the ACT (BSC).

2.5.2.2 Subgroup characteristic "age" (< 65 years versus ≥ 65 years)

The summary of results that determined the overall conclusion on added benefit is shown in Table 16. The subgroup effects by the characteristic "age" were initially disregarded, in that only those effects in which no indication or proof of an effect modification by the characteristic "age" were shown. Thereafter, it was investigated whether different conclusions for the 2 age groups arose if the results on time to first skeletal-related complication were taken into account.

Table 16: Positive and negative effects from the assessment of enzalutamide + BSC compared with BSC on the basis of outcomes in which there was no effect modification by age

Positive effects	**Negative effects**
Hint of an added benefit – extent: "major" (duration of survival: all-cause mortality)	—
Hint of an added benefit – extent: "considerable" (non-serious/non-severe symptoms: time to pain progression)	
Hint of an added benefit - extent: "non-quantifiable" (non-serious/non-severe symptoms: change in pain intensity)	
Hint of a lesser harm – extent: "non-quantifiable" (serious/severe AEs: severe AEs [CTCAE Grade ≥ 3])	
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events	

Based on the available and evaluable results, overall only positive effects remain, each with the same probability (hint). These were shown in the outcome categories "mortality", "serious/severe symptoms/late complications", "serious/severe AEs" and "non-serious/non-severe symptoms/late complications". The hint of a major added benefit in terms of overall survival is decisive for the derivation of the overall conclusion on added benefit. The extent of the added benefit for the outcomes "change in pain intensity" and "severe AEs" is non-quantifiable. Overall, without consideration of the results in which an indication of an effect modification by the characteristic "age" was produced, there is first of all a hint of a major added benefit of enzalutamide + BSC compared with BSC.

For patients < 65 years there is also a hint of a considerable added benefit and for patients ≥ 65 years a hint of a minor added benefit, in each case for the outcome "time to first skeletal-related complication". In neither case does this have any effect on the overall result (hint of a major added benefit).

Overall the characteristic "age" has no influence on the overall conclusion on added benefit.

2.5.3 Extent and probability of added benefit - Summary

For patients with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel chemotherapy, in the 2 subgroups of patients with and without visceral metastases there is added benefit of enzalutamide + BSC compared with the ACT (BSC) as shown in Table 17.

Table 17: Patient groups, ACT and extent and probability of added benefit of enzalutamide for patients with metastatic castration-resistant prostate cancer, whose disease has progressed on or after docetaxel chemotherapy

Patient group	**ACT**	**Extent and probability of the added benefit**
Patients with visceral metastases	BSC[a]	Hint of considerable added benefit
Patients without visceral metastases	BSC[a]	Hint of major added benefit
a: BSC is understood as the therapy that ensures the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care		

The overall assessment differs substantially from that of the company, which claimed proof of major added benefit for the total population of patients with metastatic castration-resistant prostate cancer, whose disease has progressed on or after docetaxel chemotherapy.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

1. Astellas Pharma. Zusatzauswertungen für Modul 4 [unpublished]. 2013.

2. Medivation. Safety and efficacy study of MDV3100 in patients with castration-resistant prostate cancer who have been previously treated with docetaxel-based chemotherapy (AFFIRM): full text view [online]. In: Clinicaltrials.gov. 15 November 2012 [accessed: 04 November 2013]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00974311.

3. Medivation. A study of patients with prostate cancer who have previously been treated with docetaxel-based chemotherapy, where patients receive either study drug or placebo [online]. In: International Clinical Trials Registry Platform. 13 May 2013 [accessed: 30 July 2013]. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=EUCTR2009-013174-41-BE.

4. Medivation. AFFIRM: a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy; study MDV3100; clinical study report [unpublished]. 2012.

5. Phung D. Statistical analysis plan for the AMNOG process [unpublished]. 2013.

6. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367(13): 1187-1197.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 4.0 [online]. 23 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Astellas. Xtandi 40 mg Weichkapseln: Fachinformation [online]. June 2013 [accessed: 4 November 2013]. URL: http://www.fachinfo.de.

4. European Medicines Agency. Xtandi 40 mg soft capsules: enzalutamide; rapporteur and co-rapporteur day 150 joint response assessment report; overview [unpublished]. 2013.

The full report (German version) is published under

https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a13_33_enzalutamid_nutzenbewertung_gemass_35a_sgb_v_dossierbewertung.3747.html